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DATE: Thursday, July 17, 2003

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L7	L6 and (liver or hepat\$)	126	L7
L6	l2 same polymorphi\$	170	L6
L5	(liver or hepat\$) and L3	364	L5
L4	l1 and L3	4	L4
L3	L2 same polymorph\$	545	L3
L2	tumor necrosis factor or TNF	22238	L2
L1	liver transplant\$ near5 (donor or donation)	50	L1

END OF SEARCH HISTORY

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=> s liver transplant? (3a) (donor or donation)  
L1 1384 LIVER TRANSPLANT? (3A) (DONOR OR DONATION)

=> s tumor necrosis factor or TNF  
L2 203588 TUMOR NECROSIS FACTOR OR TNF

=> s l2 and polymorphi  
L3 0 L2 AND POLYMORPHI

=> s l2 and polymorphi?

L4 4058 L2 AND POLYMORPHI?

=> s l1 and l4

L5 2 L1 AND L4

=> dup rem l5

PROCESSING COMPLETED FOR L5

L6 2 DUP REM L5 (0 DUPLICATES REMOVED)

=> d bib abs 1-

YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS

AN 2002:658655 CAPLUS

DN 137:196648

TI \*\*\*TNF\*\*\* -.alpha. \*\*\*polymorphism\*\*\* and genotyping for identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* \*\*\*donor\*\*\*

IN Rosen, Hugo R.

PA USA

SO U.S. Pat. Appl. Publ., 12 pp., Cont. of U.S. Ser. No. 421,987, abandoned.  
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI US 2002119468 A1 20020829 US 2001-955407 20010912

PRAI US 1999-421987 B1 19991019

AB The present invention provides a method of identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* \*\*\*donor\*\*\*. The method includes the step of detg. in an individual the presence or absence of a preferred genotype at a \*\*\*polymorphic\*\*\* site, where the preferred genotype is assocd. with altered activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\*

\*\*\*factor\*\*\*, and wherein the presence of the preferred genotype indicates that the individual is a preferred \*\*\*liver\*\*\*

\*\*\*transplant\*\*\* \*\*\*donor\*\*\*. A preferred genotype can be assocd.

with lower activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\*

such as \*\*\*TNF\*\*\* -.alpha. and can be, for example, TNF308.1. In particular, there are two alleles for \*\*\*TNF\*\*\* -.alpha. nucleotide -308 loci, TNF308.1 (common or "1" allele, with G at position -308) and TNF308.2 (rare or "2" allele, with A at position -308). The TNF308.2 allele appears to be a stronger transcriptional activator, and correlates with a more rapid, frequent and severe recurrence of hepatitis C virus infection in the recipient of a liver allograft, and hence is not a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* \*\*\*donor\*\*\* in the screening. Other \*\*\*polymorphic\*\*\* loci for other regions of \*\*\*TNF\*\*\* -.alpha. gene or other \*\*\*TNF\*\*\* genes ( \*\*\*TNF\*\*\* .beta., TNFc) are also described. The methods of the invention are useful for identifying a preferred donor liver for transplant into a HCV infected patient. The invention addnl. provides a method for selecting a preferred liver for transplantation. The invention further provides a method for limiting the recurrence of HCV infection in a liver transplant recipient.

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

AN 2001:300421 CAPLUS

DN 134:323139

TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* genotypes in methods for identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* \*\*\*donor\*\*\*

IN Rosen, Hugo R.

PA Department of Veterans Affairs Medical Center, USA

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2001028324 A1 20010426 WO 1999-US24709 19991019

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI WO 1999-US24709 19991019

AB The present invention provides a method of identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* \*\*\*donor\*\*\*. The method includes the step of detg. in an individual the presence or absence of a preferred genotype at a \*\*\*polymorphic\*\*\* site, where the preferred genotype is assocd. with altered activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\*

\*\*\*factor\*\*\*, and wherein the presence of the preferred genotype indicates that the individual is a preferred \*\*\*liver\*\*\*

\*\*\*transplant\*\*\* \*\*\*donor\*\*\*. A preferred genotype can be assocd.

with lower activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\*

such as \*\*\*TNF\*\*\* -.alpha. and can be, for example, TNF308.1. The methods of the invention are useful for identifying a preferred donor liver for transplant into a HCV infected patient. The invention addnl. provides a method for selecting a preferred liver for transplantation.

The invention further provides a method for limiting the recurrence of HCV infection in a liver transplant recipient. \*\*\*TNF\*\*\* genetic \*\*\*polymorphisms\*\*\* were detd. in donor livers, and it was found that the presence of the less common 308.2 allele in the TN- $\alpha$ . promoter correlated with a more rapid, frequent and severe recurrence of hepatitis C in the recipient of a liver allograft.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

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(FILE 'HOME' ENTERED AT 18:01:16 ON 17 JUL 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 18:01:23 ON 17 JUL 2003  
 L1 1384 S LIVER TRANSPLANT? (3A) (DONOR OR DONATION)  
 L2 203588 S TUMOR NECROSIS FACTOR OR TNF  
 L3 0 S L2 AND POLYMORPHI  
 L4 4058 S L2 AND POLYMORPHI?  
 L5 2 S L1 AND L4  
 L6 2 DUP REM L5 (0 DUPLICATES REMOVED)

=> s l4 and liver transplan?

L7 53 L4 AND LIVER TRANSPLAN?

=> dup rem l7

PROCESSING COMPLETED FOR L7

L8 35 DUP REM L7 (18 DUPLICATES REMOVED)

=> d bib abs 1-

YOU HAVE REQUESTED DATA FROM 35 ANSWERS - CONTINUE? Y/N:y

L8 ANSWER 1 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003160842 EMBASE  
 TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -.alpha. promoter  
 \*\*\*polymorphisms\*\*\* and the risk of rejection after \*\*\*liver\*\*\*  
 \*\*\*transplantation\*\*\* : A case control analysis of 210 donor-recipient  
 pairs.  
 AU Jazrawi S.F.; Zaman A.; Muhammad Z.; Rabkin J.M.; Corless C.L.; Olyaei A.;  
 Biggs A.; Ham J.; Chou S.; Rosen H.R.  
 CS Dr. H.R. Rosen, Div. of Gastroenterology/Hepatology, Portland Veterans  
 Affairs Med. Ctr., SW U.S. Veterans Hospital, Portland, OR 97207, United  
 States. hugo.rosen@med.va.gov  
 SO Liver Transplantation, (1 Apr 2003) 9/4 (377-382).  
 Refs: 32  
 ISSN: 1527-6465 CODEN: LITRFO  
 CY United States  
 DT Journal; Article  
 FS 022 Human Genetics  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 048 Gastroenterology  
 LA English  
 SL English  
 AB After orthotopic \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* (OLT),  
 allograft rejection remains an important problem and is the major reason  
 that immunosuppressive therapy must be administered. \*\*\*Tumor\*\*\*  
 \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -.alpha. ( \*\*\*TNF\*\*\* -.alpha.) is a  
 proinflammatory mediator that is central to the immune response, and  
 intragraft expression of this cytokine is increased during acute cellular  
 rejection (ACR). \*\*\*Polymorphisms\*\*\* within the \*\*\*TNF\*\*\* promoter  
 have been identified and correlated with alterations in production. The  
 aims of this study were to determine if an individual patient's propensity  
 to develop ACR is related to the presence of these genetic  
 \*\*\*polymorphisms\*\*\* (either alone or in combination) within donor and  
 recipient tissue and to determine if these \*\*\*polymorphisms\*\*\* affect  
 patient survival after OLT. The study group consisted of 210 patients who  
 underwent OLT between 1989 and 1999 with at least 6 months survival,  
 including 42 cases who had evidence of acute cellular rejection  
 (biopsy-proven, elevated enzymes, and response to increased  
 immunosuppression) and were matched 4:1 to controls (n = 168) with similar  
 age, gender, underlying liver disease, date of transplant, and baseline  
 immunosuppression. The underlying liver diseases were hepatitis C virus  
 (HCV)/alcohol (70), HCV alone (50), alcohol (30), primary biliary  
 cirrhosis (15), primary sclerosing cholangitis (15), autoimmune  
 hepatitis/cirrhosis (10), cryptogenic (15), and hepatitis B virus (HBV)  
 (5). DNA was extracted from paraffin-embedded donor and recipient liver  
 tissue (total 420 samples), amplified, and sequenced for \*\*\*TNF\*\*\*  
 single-nucleotide \*\*\*polymorphisms\*\*\* (TNFA-308 A/G and TNFA-238 A/G). We  
 found no differences between the \*\*\*TNF\*\*\* allelic distributions  
 among donors without liver disease (presumably representative of a normal  
 control population) and patients with end-stage liver disease undergoing  
 OLT. Multivariate analysis revealed no association with \*\*\*TNF\*\*\*  
 \*\*\*polymorphisms\*\*\* (within donor or recipient tissue) and rejection  
 risk or patient survival after transplantation. In this large case control  
 analysis of patients undergoing \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*  
 for diverse etiologies, \*\*\*TNF\*\*\* promoter \*\*\*polymorphisms\*\*\*  
 were not independently associated with rejection or survival.

L8 ANSWER 2 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003076253 EMBASE

TI Are cytokine gene \*\*\*polymorphisms\*\*\* related to in vitro cytokine

production profiles?

AU Warle M.C.; Farhan A.; Metselaar H.J.; Hop W.C.J.; Perrey C.; Zondervan P.E.; Kap M.; Kwekkeboom J.; Ijzermans J.N.M.; Tilanus H.W.; Pravica V.; Hutchinson I.V.; Bouma G.J.

CS G.J. Bouma, Erasmus Medical Center, Department of Surgery, Liver Transplant Research Unit, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. gerda.bouma@tiscali.nl  
 SO Liver Transplantation, (1 Feb 2003) 9/2 (170-181).

Refs: 43

ISSN: 1527-6465 CODEN: LITRFO

CY United States

DT Journal; Article

FS 022 Human Genetics

026 Immunology, Serology and Transplantation

029 Clinical Biochemistry

037 Drug Literature Index

048 Gastroenterology

LA English

SL English

AB Currently, there is much interest in the genetic basis for diseases or disease manifestations and, in particular, in whether they are related to cytokine gene \*\*\*polymorphisms\*\*\*. It has become accepted to denote such single-nucleotide \*\*\*polymorphisms\*\*\* of cytokine genes by their presumed association with high or low in vitro cytokine production. In this article, we analyze the relationship between cytokine gene \*\*\*polymorphisms\*\*\* and in vitro \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\*

\*\*\*factor\*\*\* ( \*\*\*TNF\*\*\* .alpha.), interferon gamma (IFN- $\gamma$ ), and interleukin (IL)-10 and IL-13 production, both in \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients and in healthy volunteers.

The evaluated cytokine gene \*\*\*polymorphisms\*\*\* involved \*\*\*TNF\*\*\*-A-308; \*\*\*TNF\*\*\*-d3; IFN- $\gamma$ -874; IL-10-1082, -819, and -592; and IL-13+2043, and -1055. For healthy volunteers, we observed a relationship between \*\*\*polymorphisms\*\*\* of \*\*\*TNF\*\*\*-d3 and IL-10-1082 with in vitro production of \*\*\*TNF\*\*\*.alpha. and IL-10, respectively, whereas no significant associations were found for the other tested cytokine gene \*\*\*polymorphisms\*\*\*. For \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients, no significant relationship could be established between any of the cytokine gene \*\*\*polymorphisms\*\*\* and in vitro production of corresponding cytokines. Also, we reviewed the literature for the association between cytokine gene \*\*\*polymorphisms\*\*\* and in vitro cytokine production in various patient groups and healthy volunteers. We found that the cellular sources, from which the cytokines were released into the culture supernatant, were different between studies. They were either whole blood, isolated monocytes, or peripheral blood mononuclear cells (PBMC). Also, the in vitro incubation protocol varied to a great extent between studies. This applied for the used in vitro stimulant, the concentration of a particular stimulant, and the length of the incubation period. Moreover, the study populations were either healthy individuals or very diverse patient groups. Therefore, it was impossible to evaluate whether in vitro cytokine production profiles really can be deduced from a particular cytokine gene \*\*\*polymorphism\*\*\*. Given the inconclusive findings, we propose to set up a multicenter workshop in which the relationship between certain cytokine gene \*\*\*polymorphisms\*\*\* and in vitro cytokine production is analyzed, using an identical in vitro cell culture system and study population. Furthermore, we suggest that cytokine gene \*\*\*polymorphisms\*\*\* be described by their localization within the gene or gene-promoter, rather than by their presumed in vitro cytokine production profile, to properly evaluate the relationship between cytokine gene \*\*\*polymorphisms\*\*\* and disease manifestations.

L8 ANSWER 3 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

1

AN 2003:117804 BIOSIS

DN PREV200300117804

TI Cytokine gene \*\*\*polymorphisms\*\*\* in patients infected with hepatitis B virus.

AU Ben-Ari, Ziv (1); Mor, Eytan; Papo, Orit; Kfir, Batia; Sulkes, Jaqueline; Tambar, Anat R.; Tur-Kaspa, Ran; Klein, Tirza

CS (1) Liver Institute, Rabin Medical Center, Beilinson Campus, P.O. Box 102, Petah Tikva, 49100, Israel Israel

SO American Journal of Gastroenterology, (January 2003, 2003) Vol. 98, No. 1, pp. 144-150, print.

ISSN: 0002-9270.

DT Article

LA English

AB OBJECTIVE: Cytokines play a key role in the regulation of the immune response. The maximal capacity of cytokine production varies among individuals and correlates with the \*\*\*polymorphism\*\*\* in the cytokine gene promoters. The aim of this study was to characterize gene

\*\*\*polymorphism\*\*\* in patients with chronic hepatitis B virus (HBV) infection and to determine the different patterns in patient subgroups.

METHODS: The study population consisted of 77 patients with chronic HBV infection (23 low-level HBV replicative carriers, 23 compensated high-level HBV replicative carriers, 21 decompensated \*\*\*liver\*\*\*

\*\*\*transplant\*\*\* candidates, and 10 patients with documented hepatocellular carcinoma). The genetic profile of five cytokines was analyzed by polymerase chain reaction-sequence-specific primer (SSP), and subjects were genotyped as high or low producers of \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -.alpha. and interleukin (IL)-6, and as high, intermediate, or low producers of transforming growth factor-beta1, interferon (IFN)- $\gamma$ , and IL-10 based on single nucleotide substitutions. The control group included 10 healthy individuals who

recovered from HBV infection and 48 healthy controls. RESULTS: A highly statistically significant difference in the distribution of the IFN-gamma gene \*\*\*polymorphism\*\*\* (at position +879) was observed between patients with chronic HBV infection and controls. The majority of the patients (65.2%) exhibited the potential to produce low levels of IFN-gamma (A/A genotype) compared with 37.5% of the control group ( $p=0.003$ ). Healthy individuals who recovered from HBV infection had a similar distribution of IFN-gamma gene \*\*\*polymorphism\*\*\* as the healthy controls. No statistically significant difference in IFN-gamma production was found between patients with low- and high-level HBV replication and between compensated and decompensated patients. There was also no statistically significant difference in the genetic ability to produce \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -alpha (at position -308), IL-8 (at position -174), IL-10 (at position -1082, -819, and -592), and transforming growth factor-beta1 (at position +10 and +25). CONCLUSION: These findings suggest an association between the genetic ability to produce low levels of IFN-gamma and the susceptibility to develop chronic HBV infection.

#### L8 ANSWER 4 OF 35 CAPLUS COPYRIGHT 2003 ACS

AN 2002:658655 CAPLUS

DN 137:196648

TI \*\*\*TNF\*\*\* -alpha, \*\*\*polymorphism\*\*\* and genotyping for identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor

IN Rosen, Hugo R.

PA USA

SO U.S. Pat. Appl. Publ., 12 pp., Cont. of U.S. Ser. No. 421,987, abandoned.

CODEN: USXXCO

DT Patent

LA English

FAN,CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI US 2002119468 A1 20020829 US 2001-955407 20010912

PRAI US 1999-421987 B1 19991019

AB The present invention provides a method of identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor. The method includes the step of detg. in an individual the presence or absence of a preferred genotype at a \*\*\*polymorphic\*\*\* site, where the preferred genotype is assoccd. with altered activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\*, and wherein the presence of the preferred genotype indicates that the individual is a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor. A preferred genotype can be assoccd. with lower activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* such as \*\*\*TNF\*\*\* -alpha, and can be, for example, TNF308.1. In particular, there are two alleles for \*\*\*TNF\*\*\* -alpha, nucleotide -308 loci, TNF308.1 (common or "1" allele, with G at position -308) and TNF308.2 (rare or "2" allele, with A at position -308). The TNF308.2 allele appears to be a stronger transcriptional activator, and correlates with a more rapid, frequent and severe recurrence of hepatitis C virus infection in the recipient of a liver allograft, and hence is not a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor in the screening. Other \*\*\*polymorphic\*\*\* loci for other regions of \*\*\*TNF\*\*\* -alpha, gene or other \*\*\*TNF\*\*\* genes ( \*\*\*TNF\*\*\* -beta, TNFc) are also described. The methods of the invention are useful for identifying a preferred donor liver for transplant into a HCV infected patient. The invention addnl. provides a method for selecting a preferred liver for transplantation. The invention further provides a method for limiting the recurrence of HCV infection in a \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipient.

#### L8 ANSWER 5 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

2

AN 2002:425157 BIOSIS

DN PREV200200425157

TI Investigation of promoter \*\*\*polymorphisms\*\*\* in the \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -alpha and interleukin-10 genes in \*\*\*liver\*\*\* \*\*\*transplant\*\*\* patients.

AU Fernandes, Helen (1); Koneru, Baburao; Fernandes, Neil; Hameed, Meera; Cohen, Marion C.; Raveche, Elizabeth; Cohen, Stanley

CS (1) Department of Pathology, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, MSB, Room C-578, Newark, NJ, 07103; fernande@umdnj.edu USA

SO Transplantation (Baltimore), (June 27, 2002) Vol. 73, No. 12, pp. 1886-1891. http://www.transplantjournal.com/ print.

ISSN: 0041-1337.

DT Article

LA English

AB Background: Cytokines such as \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* ( \*\*\*TNF\*\*\* -alpha and interleukin (IL)-10 play significant roles in the inflammatory and immune responses that mediate allograft rejection. The presence of a GfwdaW $\Delta$  \*\*\*polymorphism\*\*\* at position -308 in the promoter region of the \*\*\*TNF\*\*\* -alpha gene increased its transcription 6- to 7-fold. A similar \*\*\*polymorphism\*\*\* at position -1082 of the IL-10 promoter results in decreased production of IL-10 protein. In this study we have determined whether the single nucleotide \*\*\*polymorphisms\*\*\* in the promoter regions of the \*\*\*TNF\*\*\* -alpha and IL-10 genes can predict the outcome of the allograft in liver recipients. Methods: DNA was extracted from whole blood of liver recipients. The genotype of the patients was determined by polymerase chain reaction using sequence-specific primers. The level of \*\*\*TNF\*\*\* -alpha and IL-10 protein was measured by ELISA after stimulation of peripheral blood mononuclear cells with concanavalin A. Results: There was

significant correlation between acute cellular rejection and the presence of the -308A \*\*\*polymorphism\*\*\* ( $P<0.001$ ), with 8 of 13 patients with the \*\*\*TNF\*\*\* -alpha \*\*\*polymorphism\*\*\* having evidence of acute rejection. Cell stimulation studies revealed that the level of \*\*\*TNF\*\*\* -alpha protein produced by patients with liver rejection was significantly higher than for patients without rejection ( $P=0.001$ ). There were no strong associations between the presence of the IL-10 \*\*\*polymorphisms\*\*\* and rejection ( $P=0.71$ ). Conclusions: This study adds to the understanding of the role of cytokine \*\*\*polymorphisms\*\*\* in \*\*\*liver\*\*\* \*\*\*transplant\*\*\*. The data suggest that cytokine promoter \*\*\*polymorphisms\*\*\* may be a risk factor associated with allograft rejection in the liver.

#### L8 ANSWER 6 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

3

AN 2002:345267 BIOSIS

DN PREV20020345267

TI Cytokine gene \*\*\*polymorphisms\*\*\* in children successfully withdrawn from immunosuppression after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*.

AU Mazarielos, George V. (1); Reyes, Jorge; Webber, Steve A.; Thomson, Angus W.; Ostrowski, Lynn; Ahmed, Mamun; Pillage, Gina; Martell, Joan; Awad, Mohammed R.; Zeevi, Adriana

CS (1) Children's Hospital of Pittsburgh, Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, 15213 USA

SO Transplantation (Baltimore), (April 27, 2002) Vol. 73, No. 8, pp. 1342-1345. http://www.transplantjournal.com/ print.

ISSN: 0041-1337.

DT Article

LA English

AB Background: Cytokine genetic \*\*\*polymorphisms\*\*\* have been associated with transplant outcome in some experimental and clinical studies, but the cytokine profile of patients who are clinically tolerant has not been investigated. Aim: Allelic variations in \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* ( \*\*\*TNF\*\*\* -alpha, interferon (INF)-gamma, transforming growth factor (TGF)-beta1, interleukin (IL)-6, and IL-10 were evaluated in patients successfully withdrawn from immunosuppression. Methods: Pediatric \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients who were successfully withdrawn from immunosuppression (n=12) or who are on minimal immunosuppression (n=7) were genotyped. A control group of liver recipients who required maintenance immunosuppression served as a control group (n=37). Results: Compared to the control group, low \*\*\*TNF\*\*\* -alpha and high/intermediate IL-10 profiles were seen in all 12 children maintained off immunosuppression and in 6 of 7 children requiring minimal immunosuppression. Conclusion: Children successfully maintained off immunosuppression are more likely to have a genetic predisposition toward low \*\*\*TNF\*\*\* -alpha and high/intermediate IL-10 production. Children maintained on minimal immunosuppression exhibit a similar cytokine profile to those successfully weaned.

#### L8 ANSWER 7 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

4

AN 2002:247666 BIOSIS

DN PREV200200247666

TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* genetic \*\*\*polymorphisms\*\*\* and response to antiviral therapy in patients with chronic hepatitis C.

AU Rosen, Hugo R. (1); McHutchison, John G.; Conrad, Andrew J.; Lenz, Jennifer J.; Marousek, Gail; Rose, Steven L.; Zaman, Atif; Taylor, Kent; Chou, Sunwen

CS (1) Division of Gastroenterology/Hepatology, 3710 SW U.S. Veterans Hospital Road, P3-G1, Portland, OR, 97207 USA

SO American Journal of Gastroenterology, (March, 2002) Vol. 97, No. 3, pp. 714-720. http://www.elsevier.com/locate/amjgastro. print.

ISSN: 0002-9270.

DT Article

LA English

AB OBJECTIVE: Hepatitis C virus (HCV) is the major causal agent of non-A, non-B hepatitis and the leading indication for \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* worldwide. The emerging field of immunogenetics has confirmed the significant role of heritability in host immune responses to infectious pathogens. Both the major and non-major histocompatibility complex genes are increasingly identified as candidate genes hypothesized to influence the susceptibility to, or the course of, a particular disease. We hypothesized that \*\*\*polymorphisms\*\*\* within the major histocompatibility complex class III region that encode for tumor necrosis factors ( \*\*\*TNF\*\*\* -alpha and \*\*\*TNF\*\*\* -beta might be predictive of response to antiviral therapy in patients with chronic hepatitis C. METHODS: A total of 155 subjects, including 110 HCV-seropositive individuals undergoing antiviral therapy and 45 ethnically similar HCV-negative controls, were studied. The HCV-positive patients had undergone antiviral treatment with either interferon monotherapy (n=73) or in combination with ribavirin (n=37) and were categorized as either nonresponders, sustained responders, or relapsers. Sixty (55%) patients had genotype 1 (1a or 1b). Genomic DNA was extracted, followed by polymerase chain reaction amplification and sequencing for two promoter \*\*\*TNF\*\*\* -alpha variants (at positions -238 and -308), as well as restriction fragment length analysis for four \*\*\*polymorphic\*\*\* loci within the \*\*\*TNF\*\*\* -beta gene (Ncol, TNFc, aa13, aa26). RESULTS: Although there was a trend toward higher frequency of the A allele in the \*\*\*TNF\*\*\* -238 promoter among HCV-infected patients (12% vs 4%), there were no significant differences in the distribution of the genotypic

\*\*\*polymorphisms\*\*\* between patients and controls. Patients with the \*\*\*TNF\*\*\* 238 A allele had higher pretreatment viral loads as compared with patients homozygous for the wild type allele (7.2X10<sup>6</sup>-4.2X10<sup>6</sup> copies/ml vs 3.8X10<sup>6</sup>-0.34X10<sup>6</sup> copies/ml, p=0.03). However, there was no association between \*\*\*TNF\*\*\* genetic markers, including multiple haplotypic combinations, and response to therapy. In addition, there was no correlation with these \*\*\*polymorphic\*\*\* loci and histological severity of liver disease. CONCLUSIONS: Although previous work has suggested potential roles for \*\*\*TNF\*\*\* in the pathogenesis of HCV infection, we were unable to identify any link between \*\*\*TNF\*\*\* genetic \*\*\*polymorphisms\*\*\* and histological severity or response to antiviral therapy.

L8 ANSWER 8 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
AN 2002247902 EMBASE

TI Cytokine gene \*\*\*polymorphisms\*\*\* and acute human liver graft rejection.

AU Warle M.C.; Farhan A.; Metselaar H.J.; Hop W.C.J.; Perrey C.; Zondervan P.E.; Kap M.; de Rave S.; Kwekkeboom J.; Ijzermans J.N.M.; Tilanus H.W.; Pravica V.; Hutchinson I.V.; Bouma G.J.

CS Dr. G.J. Bouma, Erasmus Medical Centre Rotterdam, Department of Surgery, Liver Transplant Unit, Dr. Molewatplein 40, 3015 GD Rotterdam, Netherlands, gerda.bouma@tiscali.nl

SO Liver Transplantation, (2002) 8/7 (603-611).

Refs: 60

ISSN: 1527-6465 CODEN: LITRFO

CY United States

DT Journal; Article

FS 009 Surgery

022 Human Genetics

026 Immunology, Serology and Transplantation

037 Drug Literature Index

048 Gastroenterology

LA English

SL English

AB Interindividual differences exist in the capacity to produce cytokines. It has been reported that levels of in vitro cytokine production measured after stimulated cell culture are associated with \*\*\*polymorphisms\*\*\* in cytokine genes. Moreover, a correlation between heart, kidney, liver, and lung graft rejection or survival with cytokine gene

\*\*\*polymorphisms\*\*\* has been described. In the present study, we analyzed the association of gene \*\*\*polymorphisms\*\*\* in T helper subtype 1 (T(H)-1), T(H)-2, and regulatory-type cytokines with human liver allograft rejection. Patients who received a primary liver graft from 1992 onward and were seen at the transplant outpatient clinic since then were included on this study (n = 89). Patients were HLA typed routinely. Biopsy-proven acute rejection occurred in 41 of 89 patients. After informed consent, blood was collected and DNA was obtained. Using amplification-refractory mutation system polymerase chain reaction, the following cytokine gene \*\*\*polymorphisms\*\*\* were determined: IL-2+166, IL-2-330, IL-15+13689, IL-15-80, \*\*\*TNF\*\*\* -A-308, TNF $\delta$ 3, IFN-G+874 (T(H)-1-type cytokines), IL-4+33, IL-4-590, IL-6-174, IL-10-592, IL-10-819, IL-10-1082, IL-13+2043, IL-13-1055 (T(H)-2 type cytokines), TGF-B1+869, and TGF-B1+915 (regulatory-type cytokines). Univariate analysis showed that \*\*\*polymorphisms\*\*\* of IL-10-1082, TGF-B1+869, and HLA-DR6 were significantly related to liver graft rejection. Multiple logistic regression analysis was used to assess which variables remained significantly predictive of acute rejection. Multivariate analysis showed that TGF-B1+869 and HLA-DR6 were independently associated with the occurrence of acute rejection. These findings suggest a role for the regulatory-type cytokine transforming growth factor- $\beta$ 1 in human liver graft rejection.

L8 ANSWER 9 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2002:331561 BIOSIS

DN PREV200200331561

TI Cytokine gene \*\*\*polymorphisms\*\*\* in \*\*\*TNF\*\*\* -alpha, IFN-gamma, IL-6, IL-10 and acute rejection development in \*\*\*liver\*\*\* \*\*\*transplant\*\*\*

AU Muro, M. (1); Montes, O. (1); Minguela, A. (1); Moya-Quiles, R. (1); Marin, L. (1); Torio, A. (1); Sanchez-Bueno, F.; Garcia-Alonso, A. (1); Parrilla, P.; Alvarez-Lopez, R. (1)

CS (1) Immunology, University Hospital Virgen Arrixaca, Murcia Spain

SO European Journal of Immunogenetics, (April, 2002) Vol. 29, No. 2, pp. 163. http://www.blackwell-science.com/cgi-bin/jnlpage.asp?Journal=ejimm&File=ej imm. print.

Meeting Info.: 16th European Histocompatibility Conference Strasbourg, England, UK March 19-22, 2002

ISSN: 0960-7420.

DT Conference

LA English

L8 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2003 ACS

AN 2001:300421 CAPLUS

DN 134:323139

TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* genotypes in methods for identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor

IN Rosen, Hugo R.

PA Department of Veterans Affairs Medical Center, USA

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2001028324 A1 20010426 WO 1999-US24709 19991019  
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,  
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,  
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,  
AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,  
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI WO 1999-US24709 19991019

AB The present invention provides a method of identifying a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor. The method includes the step of detg. in an individual the presence or absence of a preferred genotype at a \*\*\*polymorphic\*\*\* site, where the preferred genotype is assocd. with altered activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\*, and wherein the presence of the preferred genotype indicates that the individual is a preferred \*\*\*liver\*\*\* \*\*\*transplant\*\*\* donor. A preferred genotype can be assocd. with lower activity of a \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* such as \*\*\*TNF\*\*\* -alpha, and can be, for example, TNF308.1. The methods of the invention are useful for identifying a preferred donor liver for transplant into a HCV infected patient. The invention addnl. provides a method for selecting a preferred liver for transplantation. The invention further provides a method for limiting the recurrence of HCV infection in a \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipient. \*\*\*TNF\*\*\* genetic \*\*\*polymorphisms\*\*\* were detd. in donor livers, and it was found that the presence of the less common 308.2 allele in the TNA-alpha promoter correlated with a more rapid, frequent and severe recurrence of hepatitis C in the recipient of a liver allograft.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
AN 2001302822 EMBASE

TI Cytokine gene \*\*\*polymorphism\*\*\* in liver allograft recipients.

AU Mor E.; Klein T.; Shabtai E.; Ben-Ari Z.; Ortegel J.W.; Micowitz R.; Tur-Kaspa R.; Tambar A.R.

CS Dr. E. Mor, Liver Transplantation Unit, Department of Transplantation, Rabin Medical Center, Petach-Tikva, Israel

SO Transplantation Proceedings, (2001) 33/6 (2941-2942).

Refs: 6

ISSN: 0041-1345 CODEN: TRPPA8

PUI S 0041-1345(01)02261-8

CY United States

DT Journal; Conference Article

FS 022 Human Genetics

026 Immunology, Serology and Transplantation

048 Gastroenterology

009 Surgery

LA English

L8 ANSWER 12 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

5

AN 2001:375215 BIOSIS

DN PREV200100375215

TI Role of cytokine gene \*\*\*polymorphism\*\*\* in hepatitis C recurrence and allograft rejection among \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients.

AU Tambar, Anat R. (1); Ortegel, John W.; Ben-Ari, Ziv; Shabtai, Eti; Klein, Tirza; Michowiz, Rachel; Tur-Kaspa, Rani; Mor, Eytan

CS (1) Department of Immunology, Rush Medical College, 1653 W Congress Parkway, 1577 Jelke, Chicago, IL, 60612: atambar@rush.edu USA

SO Transplantation (Baltimore), (May 27, 2001) Vol. 71, No. 10, pp.

1475-1480, print.

ISSN: 0041-1337.

DT Article

LA English

SL English

AB Background. Cytokines play a key role in the regulation of immune responses. The maximal capacity of cytokine production varies between individuals and was shown to correlate with \*\*\*polymorphism\*\*\* in cytokine gene promoters. The objective of this study was to analyze the role of cytokine allelic variations in susceptibility to early graft rejection episodes and recurrence of hepatitis C infection if \*\*\*liver\*\*\* \*\*\*transplant\*\*\* (LTx) recipients. Methods. The genetic profile of five cytokines was studied in 68 LTx recipients and 49 controls using polymerase chain reaction sequence specific primers. All individuals were genotyped as high or low producers of \*\*\*TNF\*\*\* -alpha and IL-6 and high, intermediate, or low producers of transforming growth factor beta (TGF-beta), interferon gamma (IFN-gamma), and interleukin 10 (IL-10) based on single nucleotide substitutions. Results. No statistically significant differences were observed between patients with or without early rejection episodes. A significant proportion of patients more prone to rejection were genotyped as having a low production profile of IL-10 compared with the control population ( $P=0.04$ ). These data are in accordance with reports regarding other solid-organ transplant recipients. Patients with no recurrence of hepatitis C had the inherent ability to

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produce higher TGF-beta levels than did patients with recurrent disease ( $P=0.042$ ). Among nonrecurrent patients, the percentage of genetically low IL-10 producers was higher than among recurrent patients ( $P=0.07$ ). Furthermore, a genetic tendency to produce higher levels of IFN-gamma was noted among LTx recipients with nonrecurrent hepatitis C than among those with recurrent hepatitis C. Conclusions. While no significant correlation was detected between particular cytokine profile and early rejection episodes, our data strongly suggest an association between cytokine gene \*\*\*polymorphism\*\*\* of TGF-beta, IL-10, and INF-gamma and recurrence of hepatitis C in LTx recipients.

L8 ANSWER 13 OF 35 CAPLUS COPYRIGHT 2003 ACS

AN 2001:719539 CAPLUS

DN 137:18568

TI Mononucleotide \*\*\*polymorphism\*\*\* of promoter region of \*\*\*TNF\*\*\* .alpha. in patients with terminal liver diseases

AU Cui, Hong; Liu, Yongfeng; He, Sanguang

CS Department of Organ Transplant, The First Clinical Medical College, China Pharmaceutical University, Shenyang, 110001, Peop. Rep. China

SO Zhonghua Yixue ZaZhi (Beijing, China) (2001), 81(15), 946-947

CODEN: CHHTAT; ISSN: 0376-2491

PB Zhonghua Yixue ZaZhishe

DT Journal

LA Chinese

AB The relationship between mononucleotide \*\*\*polymorphism\*\*\* of promoter region of \*\*\*TNF\*\*\* .alpha. and terminal liver diseases was studied. DNA was extd. from peripheral blood monocytes of 121 patients with \*\*\*liver\*\*\* \*\*\*transplant\*\*\* . The \*\*\*polymorphism\*\*\* at 308 site of promoter region of \*\*\*TNF\*\*\* .alpha. was analyzed by PCR with specific primers. The frequency of G/G, G/A, and A/A at 308 site of promoter region of \*\*\*TNF\*\*\* .alpha. in patients with \*\*\*liver\*\*\* \*\*\*transplant\*\*\* was 60, 40, and 0%. The frequency of G/G at 308 site of promoter region of \*\*\*TNF\*\*\* .alpha. in 31 patients with alc. cirrhosis, 19 patients with liver cirrhosis induced by viral infection, 18 patients with primary biliary cirrhosis, 21 patients with primary cirrhotic biliary cirrhosis, 9 patients with liver cirrhosis induced by the other factors, and 23 patients with other diseases was 25.0, 15.3, 22.2, 12.5, 5.6, and 19.4%, and that of G/A was 26.5, 16.3, 4.1, 24.5, 10.2, and 18.4%, resp. The results showed that the frequency of G/G in patients was higher than that of G/A, and \*\*\*polymorphism\*\*\* at 308 site of promoter region of \*\*\*TNF\*\*\* .alpha. may play an important role in progression of terminal liver diseases.

L8 ANSWER 14 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2001:385850 BIOSIS

DN PREV200100385850

TI Donor cytokine gene \*\*\*polymorphisms\*\*\* are associated with increased graft loss and dysfunction after transplant.

AU Gandhi, N.; Goldman, D.; Kahan, D.; Supran, S.; Saloman, R.; Delmonico, F.; O'Connor, K.; Rohrer, R.; Freeman, R. (1)

CS (1) Division of Transplant Surgery, New England Medical Center, 750 Washington Street, Boston, MA, 02111 USA

SO Transplantation Proceedings, (February March, 2001) Vol. 33, No. 1-2, pp. 827-828, print.

Meeting Info.: XVIII International Congress of the Transplantation Society Rome, Italy August 29-September 01, 2000 Transplantation Society

ISSN: 0041-1345.

DT Conference

LA English

SL English

L8 ANSWER 15 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2001431384 EMBASE

TI Etiopathogenesis of biliary atresia.

AU Sokol R.J.; Mack C.

CS Dr. R.J. Sokol, Box B290, Children's Hospital, 1056 E. 19th Ave., Denver, CO 80218, United States. sokol.ronald@tchden.org

SO Seminars in Liver Disease, (2001) 21/4 (517-524).

Refs: 58

ISSN: 0272-8087 CODEN: SLDEEE

CY United States

DT Journal; General Review

FS 004 Microbiology

005 General Pathology and Pathological Anatomy

007 Pediatrics and Pediatric Surgery

026 Immunology, Serology and Transplantation

048 Gastroenterology

LA English

SL English

AB Biliary atresia, a progressive sclerosis of the extrahepatic biliary tree that occurs only within the first 3 months of life, is one of the most common causes of neonatal cholestasis and accounts for over half of children who undergo \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*. In biliary atresia, a number of prenatal or perinatal insults to the biliary tree appear to culminate in complete obliteration of the lumen of the extrahepatic biliary tree and continued injury and sclerosis of intrahepatic bile ducts, even after portoenterostomy is successful. A minority of cases of biliary atresia may be caused by defects in morphogenesis of the bile ducts. Potential etiologies for the more common perinatal form of biliary atresia include viral infections, immune-mediated bile duct injury, and autoimmune disease involving the bile ducts. Two viruses, reovirus and rotavirus, have received increasing

attention as possible inciters of an immune-mediated injury to the biliary tree. Fas ligand upregulation and apoptosis of bile duct epithelia have been demonstrated in human specimens, as well as T-lymphocyte and macrophage activation in portal tracts. An experimental model using rotavirus infection in newborn mice has been useful in characterizing the mechanisms underlying bile duct injury. It is proposed that virally induced neoantigens displayed on biliary epithelium may play a role in initiating the immune processes involved in destruction of the extrahepatic bile duct and ongoing intrahepatic ductal injury in the perinatal form of biliary atresia. The short window of time after birth during which this disease presents suggests that immaturity of the neonatal immune system and genetic susceptibility also may be key factors. Delineation of the mechanisms underlying bile duct injury will be essential to the development of new potential therapies for this important pediatric disorder.

L8 ANSWER 16 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2001:530074 BIOSIS

DN PREV200100530074

TI Case control study of \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -alpha promoter \*\*\*polymorphisms\*\*\* for predicting outcome of \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* : An analysis of 210 donor-recipient pairs.

AU Jazrawi, Saad F. (1); Muhammad, Zofair (1); Corless, Christopher L.; Rabkin, John M.; Zaman, Atif; Chou, Sunwen; Rosen, Hugo R.

CS (1) Portland VAMC, Portland, OR USA

SO Hepatology, (October, 2001) Vol. 34, No. 4 Pt. 2, pp. 291A, print. Meeting Info.: 52nd Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 09-13, 2001 ISSN: 0270-9139.

DT Conference

LA English

SL English

L8 ANSWER 17 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2001119905 EMBASE

TI Role of cytokine gene \*\*\*polymorphisms\*\*\* in acute rejection and renal impairment after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*.

AU Jonsson J.R.; Hong C.; Purdie D.M.; Hawley C.; Isbel N.; Butler M.; Balderson G.A.; Clouston A.D.; Pandeya N.; Stuart K.; Edwards-Smith C.; Crawford D.H.; Fawcett J.; Powell E.E.

CS Dr. E.E. Powell, Clinical Training/Gastroenterologist, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia

SO Liver Transplantation, (2001) 7/3 (255-263).

Refs: 35

ISSN: 1527-6465 CODEN: LITRFO

CY United States

DT Journal; Article

FS 022 Human Genetics

026 Immunology, Serology and Transplantation

028 Urology and Nephrology

037 Drug Literature Index

038 Adverse Reactions Titles

048 Gastroenterology

LA English

SL English

AB Although immunosuppressive regimens are effective, rejection occurs in up to 50% of patients after orthotopic \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* (OLT), and there is concern about side effects from long-term therapy. Knowledge of clinical and immunogenetic variables may allow tailoring of immunosuppressive therapy to patients according to their potential risks. We studied the association between transforming growth factor- $\beta$ , interleukin-10, and \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* .alpha. ( \*\*\*TNF\*\*\* .alpha.) gene \*\*\*polymorphisms\*\*\* and graft rejection and renal impairment in 121 white \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients. Clinical variables were collected retrospectively, and creatinine clearance was estimated using the formula of Cockcroft and Gault. Biallelic \*\*\*polymorphisms\*\*\* were detected using polymerase chain reaction-based methods. Thirty-seven of 121 patients (30.6%) developed at least 1 episode of rejection. Multivariate analysis showed that Child-Pugh score ( $P=.001$ ), immune-mediated liver disease ( $P=.018$ ), normal pre-OLT creatinine clearance ( $P=.037$ ), and fewer HLA class 1 mismatches ( $P=.038$ ) were independently associated with rejection. Renal impairment occurred in 80% of patients and was moderate or severe in 39%. Clinical variables independently associated with renal impairment were female sex ( $P=.001$ ), pre-OLT renal dysfunction ( $P=.0001$ ), and a diagnosis of viral hepatitis ( $P=.0008$ ). There was a significant difference in the frequency of \*\*\*TNF\*\*\* .alpha.-308 alleles among the primary liver diseases. After adjustment for potential confounders and a Bonferroni correction, the association between the \*\*\*TNF\*\*\* .alpha.-308 \*\*\*polymorphism\*\*\* and graft rejection approached significance ( $P=.06$ ). Recipient cytokine genotypes do not have a major independent role in graft rejection or renal impairment after OLT. Additional studies of immunogenetic factors require analysis of large numbers of patients with appropriate phenotypic information to avoid population stratification, which may lead to inappropriate conclusions.

L8 ANSWER 18 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2001:249465 BIOSIS

DN PREV200100249465

TI Cytokine producing cells and gene \*\*\*polymorphism\*\*\* in \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*  
AU Santos, P. (1); Paiva, A. (1); Ballesteros, R.; Vale-Pereira, S. (1); Mareco, R. (1); Freitas, A. (1); Perdigoto, R.; Linhares-Furtado, A.; Regateiro, F. J. (1)  
CS (1) Centro de Histocompatibilidade do Centro, Coimbra Portugal  
SO European Journal of Immunogenetics, (April, 2001) Vol. 28, No. 2, pp. 253. print.  
Meeting Info.: 15th European Histocompatibility Conference Granada, Spain March 27-30, 2001  
ISSN: 0960-7420.

DT Conference  
LA English  
SL English

L8 ANSWER 19 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2001:235952 BIOSIS  
DN PREV200100235952

TI Relationship of cytokine gene \*\*\*polymorphism\*\*\* to the post-transplant outcomes.  
AU Zeevi, A. (1); Green, M. (1); Row, D. (1); Awad, M. (1); Ahmed, M. (1); Mazarielos, G. (1); Reyes, G. (1); Nalesnik, M. (1); Fung, J. (1); Webber, S. (1)  
CS (1) University of Pittsburgh, Pittsburgh USA  
SO European Journal of Immunogenetics, (April, 2001) Vol. 28, No. 2, pp. 229. print.  
Meeting Info.: 15th European Histocompatibility Conference Granada, Spain March 27-30, 2001  
ISSN: 0960-7420.

DT Conference  
LA English  
SL English

L8 ANSWER 20 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2001:517999 BIOSIS  
DN PREV200100517999

TI \*\*\*TNF\*\*\* -alpha, TGF-beta, IL-10, IL-6 and IFN-gamma gene \*\*\*polymorphism\*\*\* in acute cellular rejection after orthotopic \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*.  
AU Santos, P. (1); Ballesteros, R.; Martinho, A.; Simoes, O.; Mareco, R.; Goncalves, I.; Perdigoto, R.; Linhares-Furtado, A. J.; Regateiro, F. J.  
CS (1) Mol Genetics Lab, Histocompatibility Center, Coimbra Portugal  
SO Human Immunology, (2001) Vol. 62, No. Supplement 1, pp. S173. print.  
Meeting Info.: 27th Annual Meeting of the American Society for Histocompatibility and Immunogenetics San Francisco, California, USA October 13-17, 2001  
ISSN: 0198-8859.

DT Conference  
LA English  
SL English

L8 ANSWER 21 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2002:188548 BIOSIS  
DN PREV200200188548

TI Gender effects on clinical expression and outcome of type 1 autoimmune hepatitis: Synergisms with known autoimmune promoters.  
AU Czaja, Albert J. (1); Agarwal, Kosh; Donaldson, Peter T.  
CS (1) Mayo Clin, Rochester, MN USA  
SO Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A354-A.355. <http://www.gastrojournal.org/>. print.

Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001  
ISSN: 0016-5085.

DT Conference  
LA English

L8 ANSWER 22 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

AN 2000:244139 BIOSIS  
DN PREV200000244139

TI The effect of \*\*\*polymorphisms\*\*\* in \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* -alpha, interleukin-10, and transforming growth factor-beta1 genes in acute hepatic allograft rejection.  
AU Bathgate, Andrew J. (1); Pravica, Vera; Perrey, Chris; Therapondos, George; Plevris, John N.; Hayes, Peter C.; Hutchinson, Ian V.  
CS (1) Department of Medicine, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh, EH3 9YW UK  
SO Transplantation (Baltimore), (April 15, 2000) Vol. 69, No. 7, pp. 1514-1517.  
ISSN: 0041-1337.

DT Article  
LA English  
SL English

AB Background: The occurrence of acute rejection in orthotopic \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* is unpredictable. The role of cytokines in the process of rejection is not entirely clear. We investigated \*\*\*polymorphisms\*\*\* in the genes encoding \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* ( \*\*\*TNF\*\*\* )-alpha, interleukin

(IL)-10, and transforming growth factor (TGF)-beta1, which affect the amount of cytokine produced in vitro, in a \*\*\*liver\*\*\* \*\*\*transplant\*\*\* population to determine any association with acute rejection. Method: DNA was extracted from whole blood of \*\*\*liver\*\*\* \*\*\*transplant\*\*\* patients. After amplification with polymerase chain reactions, the \*\*\*polymorphisms\*\*\* at \*\*\*TNF\*\*\* -alpha -308, IL-10 -1082, and TGF-beta1 +869 and +915 were determined using sequence-specific oligonucleotide probes. Acute cellular rejection was a clinical and histological diagnosis. Results: Acute cellular rejection requiring treatment occurred in 68 (48%) of 144 patients. Acute cellular rejection was significantly associated with the \*\*\*TNF\*\*\* -alpha -308 A/A genotype ( $P < 0.02$ ). There was no significant association with either IL-10 or TGF-beta1 \*\*\*polymorphisms\*\*\* in acute rejection. Conclusion: Patients with a homozygous \*\*\*TNF\*\*\* -alpha -308 genotype AA are more likely to suffer from acute cellular rejection after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*.

L8 ANSWER 23 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI.

B.V.DUPLICATE 7

AN 2001027556 EMBASE

TI \*\*\*Polymorphisms\*\*\* in tumour necrosis factor .alpha., interleukin-10 and transforming growth factor .beta..1 genes and end-stage liver disease.

AU Bathgate A.J.; Pravica V.; Perrey C.; Hayes P.C.; Hutchinson I.V.  
CS Dr. A.J. Bathgate, Department of Medicine, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, United Kingdom. abathgate@ed.ac.uk  
SO European Journal of Gastroenterology and Hepatology, (2000) 12/12 (1329-1333).

Refs: 27

ISSN: 0954-691X CODEN: EJGHES

CY United Kingdom

DT Journal; Article

FS 022 Human Genetics

048 Gastroenterology

LA English

SL English

AB Objective: To determine any relationship between \*\*\*polymorphisms\*\*\*

in the genes encoding tumour necrosis factor .alpha. ( \*\*\*TNF\*\*\* .alpha.), interleukin-10 (IL-10) and transforming growth factor .beta..1 (TGF-.beta..1) and end-stage liver disease. Methods: Whole-blood samples were taken from patients attending the Scottish \*\*\*Liver\*\*\* \*\*\*Transplant\*\*\* Unit with end-stage liver disease (primary biliary cirrhosis, n = 61; alcoholic liver disease, n = 25; primary sclerosing cholangitis, n = 17; viral disease, n = 8; type 1 auto-immune hepatitis, n = 8; acute liver failure, n = 20). DNA was extracted and the \*\*\*polymorphisms\*\*\* at positions \*\*\*TNF\*\*\* -308, IL-10 -1082 and TGF-.beta..1 +869 and +915 were determined using sequence-specific oligonucleotide probes. Samples were also analysed from normal healthy controls. Results: There was a significant difference between patients with primary sclerosing cholangitis and healthy controls, with 65% of patients (11/17) possessing at least one TNF2 allele (A at position -308) compared with 38% of controls ( $P = 0.02$ ). Four of the eight patients with autoimmune hepatitis were homozygous for TNF2 while the other four were heterozygous ( $P = 0.001$ ). No significant difference between controls and patients was seen in \*\*\*polymorphisms\*\*\* for IL-10 or TGF-.beta..1. No association between genotype and Child's class was found in primary biliary cirrhosis. Conclusion: Patients with primary sclerosing cholangitis and auto-immune hepatitis are more likely to possess TNF2 than normal controls. This allele has been associated with an increased production of \*\*\*TNF\*\*\* .alpha. in vitro and may indicate a predisposition to these inflammatory conditions. .COPYRGT. 2000 Lippincott Williams & Wilkins.

L8 ANSWER 24 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2000157895 EMBASE

TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* \*\*\*polymorphisms\*\*\* and acute reflection: Proven link or provisional association.

AU Marshall S.E.; Welsh K.I.

CS S.E. Marshall, Oxford Transplant Ctr. and Nuffield, Department of Surgery, Oxford Radcliffe Hospitals, Oxford, United Kingdom

SO Transplantation, (15 Apr 2000) 69/7 (1237-1239).

Refs: 10

ISSN: 0041-1337 CODEN: TRPLAU

CY United States

DT Journal; Note

FS 022 Human Genetics

026 Immunology, Serology and Transplantation

048 Gastroenterology

LA English

L8 ANSWER 25 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

8

AN 2000:206053 BIOSIS

DN PREV200000206053

TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* genetic \*\*\*polymorphisms\*\*\* correlate with infections after renal transplantation.

AU Sahoo, Sunati; Kang, Sonya; Supran, Stacey; Saloman, Robert; Wolfe, Hubert; Freeman, Richard B. (1)

CS (1) Division of Transplant Surgery, New England Medical Center, 750 Washington Street, Boston, MA, 02111 USA

SO Transplantation (Baltimore), (March 15, 2000) Vol. 69, No. 5, pp. 880-884.

ISSN: 0041-1337.

- DT Article  
 LA English  
 SL English
- AB Background: Nonimmunosuppressed individuals possessing a NcoI restriction enzyme site in the \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* (\*\*\*TNF\*\*\* ) gene locus produce less \*\*\*TNF\*\*\* -alpha in vitro and in vivo than do individuals lacking this site. We have previously shown that this NcoI+ /low \*\*\*TNF\*\*\* -alpha genotype is independently associated with increased rates of infection for \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients. Methods: In this study, we performed polymerase chain reaction amplification and restriction fragment length \*\*\*polymorphism\*\*\* analysis of the \*\*\*TNF\*\*\* locus from 45 renal transplant recipients to determine whether the presence of the NcoI site is associated with the frequency of rejection, infection, time to rejection or infection, and patient or graft survival. Results: Twenty-six recipients were typed with the NcoI+ /low \*\*\*TNF\*\*\* -alpha genotype, whereas 19 recipients had the NcoI/high \*\*\*TNF\*\*\* -alpha genotype. Age, sex, donor type, secondary immunosuppression, use of anti-lymphocyte preparations, graft ischemia time, and year of transplant were evenly distributed in the two groups. There was no difference between the genotype groups in the rate of, or time to, rejection. In contrast, significantly more patients with the NcoI+ /low \*\*\*TNF\*\*\* -alpha site developed infections (46% vs. 10% P=0.01). In bivariable models, each controlling for donor type, ischemia time, recipient age, use of antilymphocyte agents, and secondary immunosuppression, the NcoI+ /low \*\*\*TNF\*\*\* -alpha genotype was still independently associated with increased numbers of infections (relative risk, 5.38; confidence interval, 1.20-23.8). Conclusion: We conclude that in individuals genetically predetermined to be low \*\*\*TNF\*\*\* -alpha producers, the additional inhibition of \*\*\*TNF\*\*\* -alpha production by routine immunosuppression may be excessive, rendering these individuals less able to respond to infectious stimuli. These patients may benefit from lower doses or withdrawal of corticosteroids, which are known inhibitors of \*\*\*TNF\*\*\* -alpha transcription.
- L8 ANSWER 26 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2000183259 EMBASE  
 TI \*\*\*Tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* gene promoter \*\*\*polymorphism\*\*\* and recurrent hepatitis C after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* : The missing link to pathogenesis or a casual association?  
 AU Rosen H.R.; Lenz J.J.; Rose S.L.; Rabkin J.; Corless C.L.; Taylor K.; Chou S.; Zein N.N.  
 CS Dr. N.N. Zein, Div. of Gastroenterology/Hepatology, Mayo Clinic and Mayo Foundation, 200 First St. SW, Rochester, MN 55905, United States  
 SO Liver Transplantation, (2000) 6/3 (381-383).  
 Refs: 36  
 ISSN: 1527-6465 CODEN: LITRFO  
 CY United States  
 DT Journal; Note  
 FS 009 Surgery  
 022 Human Genetics  
 048 Gastroenterology  
 LA English
- L8 ANSWER 27 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI.  
 B.V.DUPLICATE 9  
 AN 2001126722 EMBASE  
 TI Autoimmune liver disease.  
 AU Czaja A.J.  
 CS Dr. A.J. Czaja, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905, United States  
 SO Current Opinion in Gastroenterology, (2000) 16/3 (262-270).  
 Refs: 31  
 ISSN: 0267-1379 CODEN: COGAEK  
 CY United States  
 DT Journal; General Review  
 FS 006 Internal Medicine  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 048 Gastroenterology  
 LA English  
 SL English
- AB Regional differences in the manifestations of autoimmune hepatitis underscore the importance of genetic and/or environmental factors in its expression. The -308 \*\*\*polymorphism\*\*\* of \*\*\*TNF\*\*\* -A increases susceptibility to type 1 autoimmune hepatitis; HLA DRB1\*13 is an important risk factor in South America; and DRB1\*07 characterizes type 2 autoimmune hepatitis. Minocycline and mesalazine can trigger the disease, and interferon therapy can accentuate autoimmune manifestations. Autoimmune cholangitis in Japan is similar to primary biliary cirrhosis, and assays for carbonic anhydrase II lack diagnostic specificity. Perinuclear antineutrophil cytoplasmic antibodies are reactive to diverse nuclear antigens, but high mobility nonhistone chromosomal proteins may be important targets in autoimmune hepatitis. T cells can cross-react with viral and host peptides, and the candidacy of glutathione S-transferases as target autoantigens has been weakened. A murine model of PBC will be useful in studying mechanisms of autoreactivity, and cyclosporine has shown promise in the treatment of children with autoimmune hepatitis. Recurrence after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* is common, and it may require retransplantation. The human transplantation model will be valuable in understanding the host- and organ-specific contributions to disease expression. COPYRGHT. 2000 Lippincott Williams & Wilkins. Inc.
- L8 ANSWER 28 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:503767 BIOSIS  
 DN PREV200000503767  
 TI The role of cytokine gene \*\*\*polymorphisms\*\*\* in renal impairment after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* .  
 AU Jonson, Julie R. (1); Hong, Cui (1); Isbel, Nicky; Hawley, Carmel; Butler, Maree; Purdie, David M.; Pandeya, Nirmala; Balderson, Glenda A.; Clouston, Andrew D.; Edwards-Smith, Catherine J.; Lynch, Stephen V.; Powell, Elizabeth E.  
 CS (1) Univ of Queensland, Brisbane, QLD Australia  
 SO Hepatology, (October, 2000) Vol. 32, No. 4 Pt. 2, pp. 254A. print.  
 Meeting Info.: 51st Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA October 27-31, 2000 American Association for the Study of Liver Diseases ISSN: 0270-9139.
- DT Conference  
 LA English  
 SL English
- L8 ANSWER 29 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:503766 BIOSIS  
 DN PREV200000503766  
 TI The role of cytokine gene \*\*\*polymorphisms\*\*\* in acute rejection after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* .  
 AU Hong, Cui (1); Powell, Elizabeth E. (1); Balderson, Glenda A. (1); Clouston, Andrew D. (1); Purdie, David M.; Pandeya, Nirmala; Edwards-Smith, Catherine J.; Stuart, Katherine A.; Crawford, Darrell Hg.; Fawcett, Jonathan; Lynch, Stephen V.; Jonson, Julie R.  
 CS (1) Univ of Queensland, Brisbane, QLD Australia  
 SO Hepatology, (October, 2000) Vol. 32, No. 4 Pt. 2, pp. 242A. print.  
 Meeting Info.: 51st Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA October 27-31, 2000 American Association for the Study of Liver Diseases ISSN: 0270-9139.
- DT Conference  
 LA English  
 SL English
- L8 ANSWER 30 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:170522 BIOSIS  
 DN PREV200000170522  
 TI Cytokine profiles in relation to acute \*\*\*liver\*\*\* \*\*\*transplant\*\*\* rejection.  
 AU Warle, M. C. (1); Perrey, C.; Metselaar, H. J.; Farhan, A.; van der Plas, A. J. (1); Kap, M. (1); Hop, W. C. J.; de Rave, S.; Kwekkeboom, J.; Zondervan, P. E.; Uzermans, J. N. M. (1); Tilanus, H. W. (1); Pravica, V.; Hutchinson, I. V.; Bouma, G. J. (1)  
 CS (1) Liver Transplant Research Unit, Surgery, Erasmus Medical Centre Rotterdam, Rotterdam Netherlands  
 SO Human Immunology., (2000) Vol. 61, No. Suppl. 1, pp. S139.  
 Meeting Info.: 14th European Histocompatibility Conference. Montpellier, France April 04-07, 2000  
 ISSN: 0198-8859.
- DT Conference  
 LA English  
 SL English
- L8 ANSWER 31 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 20000188532 EMBASE  
 TI The US-Japan Cooperative Medical Science Program Tuberculosis-Leprosy Panel's 34th Annual Research Conference, San Francisco, California, 27-30 June 1999: Conference report.  
 AU Ginsberg A.M.  
 SO Tubercle and Lung Disease, (2000) 80/2 (85-108).  
 Refs: 0  
 ISSN: 0962-8479 CODEN: TLDIEP  
 CY United Kingdom  
 DT Journal; Conference Article  
 FS 004 Microbiology  
 005 General Pathology and Pathological Anatomy  
 006 Internal Medicine  
 015 Chest Diseases, Thoracic Surgery and Tuberculosis  
 037 Drug Literature Index  
 LA English
- L8 ANSWER 32 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE  
 10  
 AN 2000:89974 BIOSIS  
 DN PREV200000089974  
 TI Donor \*\*\*polymorphism\*\*\* of \*\*\*tumor\*\*\* \*\*\*necrosis\*\*\* \*\*\*factor\*\*\* gene: Relationship with variable severity of hepatitis C recurrence after \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* .  
 AU Rosen, Hugo R. (1); Lenz, Jennifer J.; Rose, Steven L.; Rabkin, John; Corless, Christopher L.; Taylor, Kent; Chou, Sunwen  
 CS (1) Division of Gastroenterology/Hepatology, 3710 Southwest U.S. Veterans Hospital Road, P3-G1, Portland, OR, 97207 USA  
 SO Transplantation (Baltimore), (Dec. 27, 1999) Vol. 68, No. 12, pp. 1898-1902.

ISSN: 0041-1337.

DT Article  
LA English  
SL English

AB Background: Hepatitis C-related liver failure is the leading indication for "liver" "transplantation" worldwide. Although histologic recurrence is identified in the majority of patients, the spectrum of allograft injury is wide. To date, most studies have focused on the contribution of immunosuppression and viral factors. We hypothesized that the allograft plays a significant role in determining timing and severity of hepatitis C virus (HCV) recurrence. The purpose of this analysis was to determine if genetic "polymorphisms" of the "tumor" "necrosis" "factor" ( "TNF" ) locus were associated with the highly variable severity of HCV recurrence. Methods: Thirty-one HCV-seropositive "liver" "transplant" recipients with long-term follow-up were studied. Genomic DNA was extracted from archived donor spleens which corresponded to each patient. We performed polymerase chain reaction amplification, followed by sequencing for two promoter "TNF"-alpha variants (at positions -238 and -308), and restriction fragment length analysis for four "polymorphic" loci within the "TNF"-beta gene (NcoI, TNFc, aa13, and aa26). Results: The relative prevalence of "polymorphisms" corresponded to distributions previously reported in normal control populations. Twenty-two of 31 (71%) patients received a donor liver homozygous for the wild type allele (TNF1) at the -308 "TNF"-alpha promoter region. The interval to histologic recurrence was significantly shorter and severity of HCV allograft hepatitis was significantly greater in patients with one or two TNF308.2 alleles. At last follow-up biopsy, 5 of 9 (56%) patients with a TNF308.2 donor liver had evidence of severe histological activity index as compared to 2 of 22 (9%) of patients receiving a donor liver homozygous for the TNF1 allele ( $P=0.01$ ). There was no correlation between rejection rates and the presence of any "TNF"-alpha or "TNF"-beta alleles. "TNF"-beta

"polymorphisms" within the donor liver did not correlate with severity of HCV recurrence. Conclusions: The donor "TNF"-alpha promoter genotype may influence the inflammatory response to HCV reinfection of the graft and contribute to accelerated graft injury. If the association between this genetic marker (TNF308.2) and disease progression is confirmed, it could improve our understanding of HCV pathogenesis and influence donor selection and patient management.

L8 ANSWER 33 OF 35 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
AN 2000003445 EMBASE

TI Erratum: "Tumor" "necrosis" "factor" genetic "polymorphisms" correlate with infections after "liver" "transplantation" (Transplantation (April 15, 1999) 67:7 (1005-1010)).

AU Freeman R.B.  
SO Transplantation, (15 Dec 1999) 68/11 (1823).  
ISSN: 0041-1337 CODEN: TRPLAU

CY United States  
DT Journal; Errata  
FS 009 Surgery  
LA English

L8 ANSWER 34 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

11

AN 1999:268914 BIOSIS  
DN PREV199900268914

TI "Tumor" "necrosis" "factor" genetic polymorphisms correlate with infections after "liver" "transplantation".

AU Freeman, Richard B., Jr. (1); Tran, Cam-Ly; Mattoli, Jessica; Patel, Ketaky; Supran, Stacey; Basile, Frank G.; Krishnamurthy, Savitri; Aihara, Rie; NEMC TNF Study Group

CS (1) Division of Transplant Surgery, New England Medical Center, 750 Washington Street, Boston, MA, 02111 USA

SO Transplantation (Baltimore), (April 15, 1999) Vol. 67, No. 7, pp. 1005-1010.  
ISSN: 0041-1337.

DT Article  
LA English  
SL English

AB "Tumor" "necrosis" "factor" -alpha ( "TNF" -alpha) is a pro-inflammatory mediator of the immune response to alloigenic and infectious stimuli. Non-immunosuppressed individuals possessing a NcoI restriction enzyme site in the "TNF" gene locus produce less "TNF" -alpha in vitro and in vivo compared with individuals lacking this restriction site. We performed polymerase chain reaction amplification and restriction enzyme fragment length analysis of the "TNF" locus from 86 "liver" "transplant" recipients to determine if presence of the NcoI site is associated with the frequency of rejection or infection, time to rejection or infection, and patient and graft survival. We controlled for recipient primary diagnosis, age, sex, United Network for Organ Sharing status, year of transplant, type of immunosuppression, use of anti-lymphocyte agents, and graft ischemia time. Fifty-six recipients possessed the NcoI+ /low "TNF" -alpha genotype and 30 were NcoI-/high "TNF" -alpha genotype. In the first year after transplant, there were no significant differences in the frequency, or time to first rejections or the overall number of rejection episodes between the two genotypes. NcoI+/low "TNF" -alpha genotype recipients had significantly more infections (1.52 vs. 0.87,  $P=0.014$ ). In a linear regression, multivariate model controlling for all marginally

significant variables, the NcoI+/low "TNF" -alpha genotype was still associated with significantly more infections ( $P=0.0031$ ). Patient and graft survival were equal for the two groups. One implication of this study, in individuals genetically predetermined to be low "TNF" -alpha producers, is that additional inhibition of "TNF" -alpha production by routine immunosuppression may be excessive, rendering these individuals less able to respond to infectious stimuli. These patients may benefit from lower doses or withdrawal of corticosteroids.

L8 ANSWER 35 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 1997:535527 BIOSIS  
DN PREV199799834730

TI A study of cytokine genetic "polymorphism" in a "liver"

"transplantation" population.

AU Bathgate, A. J.; Plevris, J. N.; Dollinger, M.; Hayes, P.; Sinnott, P.; Pravica, V.; Hutchinson, I.

CS Scottish Liver Transplant Unit, Edinburgh UK

SO Hepatology, (1997) Vol. 26, No. 4 PART 2, pp. 241A.

Meeting Info.: 48th Annual Meeting of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 7-11, 1997

ISSN: 0270-9139.

DT Conference; Abstract

LA English

=> s liver transplant?

L9 45146 LIVER TRANSPLANT?

=> s i9 and review

L10 4256 L9 AND REVIEW

=> dup rem l10

PROCESSING IS APPROXIMATELY 50% COMPLETE FOR L10

PROCESSING IS APPROXIMATELY 84% COMPLETE FOR L10

PROCESSING COMPLETED FOR L10

L11 3648 DUP REM L10 (608 DUPLICATES REMOVED)

=> d bib abs

L11 ANSWER 1 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2003220096 EMBASE

TI Responding to organ failure in HIV-infected patients.

AU Roland M.E.; Havlir D.V.

SO New England Journal of Medicine, (5 Jun 2003) 348/23 (2279-2281).

Refs: 2

ISSN: 0028-4793 CODEN: NEJMAG

CY United States

DT Journal; General Review

FS 004 Microbiology

005 Internal Medicine

009 Surgery

037 Drug Literature Index

LA English

=> d bib abs 2-10

L11 ANSWER 2 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2003164860 EMBASE

TI Skin cancers after organ transplantation.

AU Euvrard S.; Kanitakis J.; Claudy A.

CS Dr. S. Euvrard, Department of Dermatology, Edouard Herriot Hospital (Pav. R), Place d'Arson val, 69437 Lyons Cedex 03, France.

sylvie.euvrard@numericable.fr

SO New England Journal of Medicine, (24 Apr 2003) 348/17 (1681-1691).

Refs: 100

ISSN: 0028-4793 CODEN: NEJMAG

CY United States

DT Journal; General Review

FS 006 Internal Medicine

009 Surgery

016 Cancer

037 Drug Literature Index

038 Adverse Reactions Titles

LA English

L11 ANSWER 3 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2003257825 EMBASE

TI Infection with Listeria monocytogenes following orthotopic "liver" "transplantation": Case report and "review" of the literature.

AU Rettali C.A.; Speeg K.V.

CS Dr. C.A. Rettali, Dept. of Gastroenterol./Nutrition, MC 7878, Univ. TX Hlth. Sci. Ctr. S. Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, United States. macare@aol.com

SO Transplantation Proceedings, (2003) 35/4 (1485-1487).

Refs: 19

ISSN: 0041-1345 CODEN: TRPPAB

CY United States

DT Journal; Article

FS 004 Microbiology

009 Surgery

- 037 Drug Literature Index  
 048 Gastroenterology  
 LA English  
 SL English  
 AB Infection with Listeria monocytogenes is rare with a reported annual incidence of 4.4 cases/million individuals. Epidemiological data have identified certain groups to be higher risk of developing listeriosis, including neonates, pregnant women, adults older than 60 years of age, individuals afflicted with hematologic malignancies, acquired immunodeficiency syndrome, cirrhosis, and those receiving corticosteroid therapy and organ transplants. Within this last group, multiple cases have been described following bone marrow and renal transplantation, but only a few following \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*. We report a case of a 66-year-old woman presenting with Listeria monocytogenes bacteremia at 32 months following orthotopic \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*
- L11 ANSWER 4 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003225669 EMBASE  
 TI A practice guideline on Wilson disease.  
 AU Roberts E.A.; Schilsky M.L.  
 CS Dr. E.A. Roberts, Division of Gastroenterology, Hospital for Sick Children, Black Family Foundation Wing, 555 University Ave., Toronto, Ont. M5G 1X8, Canada. eroberts@sickkids.ca  
 SO Hepatology, (1 Jun 2003) 37/6 (1475-1492).  
 Refs: 208  
 ISSN: 0270-9139 CODEN: HPTLD  
 CY United States  
 DT Journal; General Review  
 FS 006 Internal Medicine  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 048 Gastroenterology  
 LA English
- L11 ANSWER 5 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003257735 EMBASE  
 TI Adult and pediatric \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* for autoimmune hepatitis.  
 AU Heffron T.G.; Smallwood G.A.; Oakley B.; Pillen T.; Welch D.; Connor K.; Martinez E.; Romero R.; Stieber A.C.  
 CS G.A. Smallwood, Emory University Hospital, School of Medicine, Office #EGH22, 1364 Clifton Road, NE, Atlanta, GA 30322, United States. greg\_smallwood@emory.org  
 SO Transplantation Proceedings, (2003) 35/4 (1435-1436).  
 Refs: 3  
 ISSN: 0041-1345 CODEN: TRPPA8  
 CY United States  
 DT Journal; Article  
 FS 009 Surgery  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 048 Gastroenterology  
 LA English  
 SL English  
 AB Background. Due to the early age that pediatric patients with autoimmune hepatitis (AIH) are transplanted, it is theorized that older AIH patients may have different outcomes than pediatric patients following \*\*\*liver\*\*\* \*\*\*transplantation\*\*\*. Methods This is a retrospective \*\*\*review\*\*\* of both the adult and pediatric \*\*\*liver\*\*\* \*\*\*transplant\*\*\* programs consisting of 56 patients. Rejection and recurrence of AIH were determined by biopsy. Results The autoimmune patient having rejection episodes had a 1.76-fold increase in relative risk to develop autoimmune recurrence when compared to patients without rejection [RR = 1.76; 95% CIR (1.08, 2.86)]. The pediatric group had a 6.62-fold increase in relative risk to develop colitis following \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* [RR = 6.62; 95% C.I.R.R. (1.36, 32.13); P = .02]. Mean days to recurrence of AIH were similar in both groups (1384.+- 1074 vs 936; P = NS). There were more hospitalized days in the pediatric group compared to the adults (20.5.+- 13.3 days vs 51.7.+- 22.2 days, P = .039). OKT-3 was rarely used (n = 5) in either group (9.3% vs 7.7%, P = NS) and was not correlated with which patients would be weaned from steroids or recurrence. Conclusions Based on this \*\*\*review\*\*\*, pediatric patients were more likely to develop ulcerative colitis following \*\*\*liver\*\*\* \*\*\*transplantation\*\*\* and they incurred longer hospital stays than adults. The adult group was more likely to be weaned from steroids, with AIH recurrence unrelated to weaning.
- L11 ANSWER 6 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003251530 EMBASE  
 TI Tacrolimus: A further update of its use in the management of organ transplantation.  
 AU Scott L.J.; McKeage K.; Keam S.J.; Plosker G.L.  
 CS L.J. Scott, Adis International Limited, 41 Centorion Drive, Mairangi Bay, Auckland 10, New Zealand. demail@adis.co.nz  
 SO Drugs, (2003) 63/12 (1247-1297).  
 Refs: 261  
 ISSN: 0012-6667 CODEN: DRUGAY  
 CY New Zealand  
 DT Journal; General Review  
 FS 026 Immunology, Serology and Transplantation
- 030 Pharmacology  
 036 Health Policy, Economics and Management  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB Extensive clinical use has confirmed that tacrolimus (Prograf,RTM.) is a key option for immunosuppression after transplantation. In large, prospective, randomised, multicentre trials in adults and children receiving solid organ transplants, tacrolimus was at least as effective or provided better efficacy than cyclosporin microemulsion in terms of patient and graft survival, treatment failure rates and the incidence of biopsy-proven acute and corticosteroid-resistant rejection episodes. Notably, the lower incidence of rejection episodes after renal transplantation in tacrolimus recipients was reflected in improved cost effectiveness. In bone marrow transplant (BMT) recipients, the incidence of tacrolimus grade II-IV graft-versus-host disease was significantly lower with tacrolimus than cyclosporin treatment. Efficacy was maintained in renal and \*\*\*liver\*\*\* \*\*\*transplant\*\*\* recipients after total withdrawal of corticosteroid therapy from tacrolimus-based immunosuppression, with the incidence of acute rejection episodes at up to 2 years' follow-up being similar with or without corticosteroids. Tacrolimus provided effective rescue therapy in transplant recipients with persistent acute or chronic allograft rejection or drug-related toxicity associated with cyclosporin treatment. Typically, conversion to tacrolimus reversed rejection episodes and/or improved the tolerability profile, particularly in terms of reduced hyperlipidaemia. In lung transplant recipients with obliterative bronchiolitis, conversion to tacrolimus reduced the decline in and/or improved lung function in terms of forced expiratory volume in 1 second. Tolerability issues may be a factor when choosing a calcineurin inhibitor. Cyclosporin tends to be associated with a higher incidence of significant hypertension, hyperlipidaemia, hirsutism, gingivitis and gum hyperplasia, whereas the incidence of some types of neurotoxicity, disturbances in glucose metabolism, diarrhoea, pruritus and alopecia may be higher with tacrolimus treatment. Renal function, as assessed by serum creatinine levels and glomerular filtration rates, was better in tacrolimus than cyclosporin recipients at up to 5 years' follow-up. Conclusion: Recent well designed trials have consolidated the place of tacrolimus as an important choice for primary immunosuppression in solid organ transplantation and in BMT. Notably, in adults and children receiving transplants, tacrolimus-based primary immunosuppression was at least as effective or provided better efficacy than cyclosporin microemulsion treatment in terms of patient and graft survival, treatment failure and the incidence of acute and corticosteroid-resistant rejection episodes. The reduced incidence of rejection episodes in renal transplant recipients receiving tacrolimus translated into a better cost effectiveness relative to cyclosporin microemulsion treatment. The optimal immunosuppression regimen is ultimately dependent on balancing such factors as the efficacy of the individual drugs, their tolerability, potential for drug interactions and pharmacoeconomic issues.
- L11 ANSWER 7 OF 3648 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 AN 2003191443 EMBASE  
 TI Transplantation of organs: Natural limitations, possible solutions - A UK perspective.  
 AU Rudge C.J.  
 CS C.J. Rudge, UK Transplant, BS 34 8 RR, Bristol, United Kingdom. chris.rudge@uktransplant.uhsouk  
 SO Transplantation Proceedings, (2003) 35/3 (1149-1150).  
 ISSN: 0041-1345 CODEN: TRPPA8  
 CY United States  
 DT Journal; Conference Article  
 FS 009 Surgery  
 017 Public Health, Social Medicine and Epidemiology  
 LA English  
 SL English  
 AB While the outcome following organ transplantation in the United Kingdom has never been better, the waiting list has never been longer and the organ shortage is now the most pressing issue. UK Transplant has invested in four initiatives to promote donor and transplant numbers: coordinating the coordinators, establishing donor liaison posts, improving living donor coordination, and encouraging non-heart-beating donation. The Potential Donor Audit to be introduced as soon as possible will clarify the likely maximum number of heart-beating donors. A major \*\*\*review\*\*\* of the legal framework covering donation and transplantation in England and Wales is currently underway. It is hoped that in due course the benefits of these initiatives will be translated into a rise in both donor and transplant numbers.
- L11 ANSWER 8 OF 3648 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2003:275111 BIOSIS  
 DN PREV200300275111  
 TI Posttransplant lymphoproliferative disorders presenting at sites of previous surgical intervention.  
 AU Doria, Cataldo (1); Marino, Ignazio R.; Scott, Victor L.; Jaffe, Ronald; Minervini, Marta I.; Zajko, Albert; Nalesnik, Michael A.  
 CS (1) Thomas E. Starzl Transplantation Institute, University of Pittsburgh, 3601 Fifth Avenue, 4th Floor, Falk Clinic, Pittsburgh, PA, 15213, USA. doria@ISMETT.edu USA  
 SO Transplantation (Hagerstown), (April 15 2003) Vol. 75, No. 7, pp. 1066-1069, print.

